

large number of influenza viruses from different hosts. In conclusion, some of the questions that need to be addressed in pandemic influenza include the following:

- Can an entire avian influenza virus adapt directly in a human, or is reassortment necessary to generate a pandemic strain?
- Does adaptation of an avian influenza virus to humans require an intermediate host?
- Can all possible subtypes of avian influenza virus reassort to form functional human pandemic strains, or are there biological limitations to particular HA and NA subtypes?
- A novel HA seems to be required for a pandemic strain; what about the other gene segments?
- Can genetic changes be mapped to “virulence”?
- Can features of virulence be separated from the host in question? Can the viral genetic component of human virulence be modeled in experimental animal or in vitro systems?
- What molecular changes are necessary for avian strains to adapt to mammals, and to humans in particular?
- Can host-adaptive changes (genetic fingerprints) be used to trace the evolution of a pandemic strain through intermediate hosts?

Unless we make progress in understanding these and other issues involving the complex ecology and biology of influenza viruses, we will face the risk of revisiting the past in our future.

#### PANDEMIC INFLUENZA AND MORTALITY: PAST EVIDENCE AND PROJECTIONS FOR THE FUTURE<sup>5</sup>

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## SUMMARY

Pandemic influenza is often thought of as a tornado—a sudden disaster that arrives with little warning and does its worst in a relatively short time. Only three of these calamities occurred in the twentieth century. Their mortality impact ranged from devastating (the 1918 “Spanish” A(H1N1) influenza) to moderate (the 1957 Asian A(H2N2) pandemic) to mild (the 1968 “Hong Kong” A(H3N2) virus). In this paper we review the “pandemic age shift,” a signature change of mortality impact from the elderly to younger age groups that has occurred during each of these pandemics. We also suggest that the “tornado” paradigm may not be completely apt, in that past pandemics have given epidemiologic warning signs of their arrival, and generally play out over several years.

For the 1918 Spanish influenza pandemic, a new study by Olson et al. documents substantial mortality impact during a pandemic “herald wave” in early spring of 1918 in New York City, and a general lack of increased pandemic mortality in those over 45 years of age. For the 1957 pandemic, a classic study documented that the emerging H2N2 influenza virus caused substantial excess mortality during the first three seasons it was in circulation. The 1968 pandemic mortality impact was only “smoldering” in Europe during the first season and did not break into open flame until the next season, during which the majority of mortality impact occurred. Although mortality caused by the 1968 pandemic virus was unimpressive relative to surrounding severe epidemics, the age shift signature sets it apart. Furthermore, antibodies to H3-like antigens—the result of exposure to these antigens in childhood prior to 1892—relatively protected people aged 77 years and older.

Because our experience with pandemic influenza is so limited, it is difficult to predict the mortality impact of future pandemics except to say that the likely range is wide (from ~20 to ~500 deaths per 100,000 population) and that those under 65 years of age will account for a high proportion of the deaths. It may be helpful to think of pandemic mortality impact as the sum of influenza-related deaths that occur over several seasons dominated by the emerging virus until the pandemic age shift pattern gives way to “business as usual,” which typically occurs after a decade or less.

The good news from epidemiological studies for pandemic preparedness planning is that past pandemics gave significant warning signs of their arrival. In 1918, a pandemic herald wave occurred 6 months or more before the majority of mortality impact the following fall. The Asian H2N2 influenza virus was characterized by early summer, 1957, but significant mortality in the United States did not occur until October. In 1968, the pandemic wave of mortality in Europe crested a full year after the pandemic strain first arrived. Furthermore, in both the 1957 and 1968 pandemics,

much of the total impact occurred as a series of smaller “twisters” in the first several seasons after its emergence, before the total population had been affected. These facts suggest that there may well be sufficient time for production and distribution of vaccine and antiviral drugs to prevent much of the mortality impact of the next pandemic, and that these medical interventions will continue to play an important role in limiting “pandemic” mortality for years after the pandemic season. Finally, the pandemic age shift documented for all pandemics studied begs the crucial question of who should be given first priority for vaccine and antivirals, should these be in short supply in the early phase of a pandemic.

### The Charge: Using Lessons from Past Pandemics to Help Project the Impact of Future Pandemics

In the case of pandemics, we are planning for the equivalent of a tornado . . . rare and completely unpredictable until the last minute, when a “weather watch” (e.g., pandemic alert) appears on the TV screen (Kilbourne, 1997).

The lesson of the history of pandemics appears to be that at least the initial attack may sometimes occur with gentleness and thus may afford a substantial breathing space for the preparation and use of specific vaccine (Stuart-Harris, 1970).

Why worry about pandemics of the past? Three influenza pandemics occurred in the twentieth century, and the patterns and magnitude of pandemic mortality are the only impact data available for all three of these events (Table 1-1). We believe, therefore, that continued epidemiological

**TABLE 1-1** Mortality Impact in the Three Pandemics of the Twentieth Century in the United States

	Antigenic Shift (Pandemic Event)	Number of Excess Deaths in the Pandemic Season (All-Cause Deaths)	Total Excess Mortality Rate per 100,000 Population (Crude) (All-Cause Deaths)
1918–1919 A(H1N1)	H + N (All novel virus?)	~ 500,000	530
1957–1958 A(H2N2)	H + N	~ 60,000	40
1968–1969 A(H3N2)	H only	~ 40,000	18

analyses of historic mortality data and sero-archaeology—the study of stored serum samples to uncover when specific influenza antigens were circulating—can expand our understanding of pandemic mortality patterns and severity, and that such studies will greatly aid public health planning for pandemic influenza.

In this review, we present the story of pandemic influenza as seen through the lens of epidemiology. For the 1968 pandemic we present data comparing the mortality impact internationally—and highlight the still unexplained finding of “smoldering” pandemic activity in Europe. We review more recent efforts to characterize the signature “age shift” of pandemic influenza and highlight the value of sero-archaeology as a tool to understand what we call “the virtues of antigenic sin”—protection derived from exposure in childhood to influenza H-antigens that are recycled in later pandemic viruses. We revisit a classic study of the 1957 pandemic that analyzes age-specific mortality data from the United States, which shows that most of the mortality was spread over three seasons; we also compare the age-specific mortality impact in the United States to that in Japan. For the 1918 pandemic, we present a study of newly uncovered mortality data from New York City that tells a fetching story about a herald wave and the sparing of the elderly (Olson et al., 2004).

These efforts to study the epidemiology of past pandemic impact on mortality are akin to the efforts by virologists who, in the interest of predicting the future, are hard at work identifying and studying preserved human and animal virus specimens from the 1918 Spanish flu pandemic (Reid and Taubenberger, 2003). But instead of molecular clues to viral pathogenicity and recombination, mortality data provides some important insights into how the pandemic evolves over time, and which age groups are at highest risk for severe outcomes. First, a future pandemic may not appear as a completely unpredictable “tornado” that hits hard the first season and leaves little time for production and distribution of vaccines and antivirals. It is certainly true that, like a tornado, no one can predict precisely when a new pandemic strain might emerge. However, studies of past pandemics show that the next pandemic may well not do its worst in the first season. Instead, historical evidence shows that there can be herald waves or smoldering activity during the first season in which the pandemic influenza virus emerges, suggesting that the preparation time for pandemic vaccines and antivirals might be longer than a few months. Second, pandemic impact cannot be discussed without speaking of age. During a pandemic, the younger population is at substantially increased risk relative to non-pandemic influenza seasons; in some pandemics, this sparing of the elderly may occur as a consequence of antigen recycling. The pandemic age shift has important consequences for thinking about how best to protect the population and minimize years of life lost to future pandemic influenza.

### The Pandemic Age Shift: A Signature of Pandemic Mortality Impact

It has previously been demonstrated that all three pandemics of this century were characterized by a shift in the age distribution of deaths (Simonsen et al., 1998). The younger population (in that study, persons under 65 years of age) experienced a sharply elevated mortality risk and accounted for a markedly increased fraction of all influenza-related deaths. As we will discuss below, the 1968 pandemic age shift pattern was exacerbated by the protection of the very elderly by virtue of their experience with H3 antigens as children (Simonsen et al., 2003). For the 1968 pandemic, then, the observed age shift was due to a combination of increased risk among the young and decreased risk among the elderly (Simonsen et al., 2003).

During the 1957 A(H2N2) Asian pandemic in the United States, nearly 40 percent of all influenza-related deaths occurred in the younger population under 65 years of age. The proportion of deaths among people under age 65 that occurred during A(H2N2) epidemics dropped to 5 percent by 1968, when circulation of this virus ceased. In the 1968 A(H3N2) pandemic, this proportion was approximately 50 percent, but declined to less than 10 percent over the next decade (Figure 1-6) (Simonsen et al., 2003).

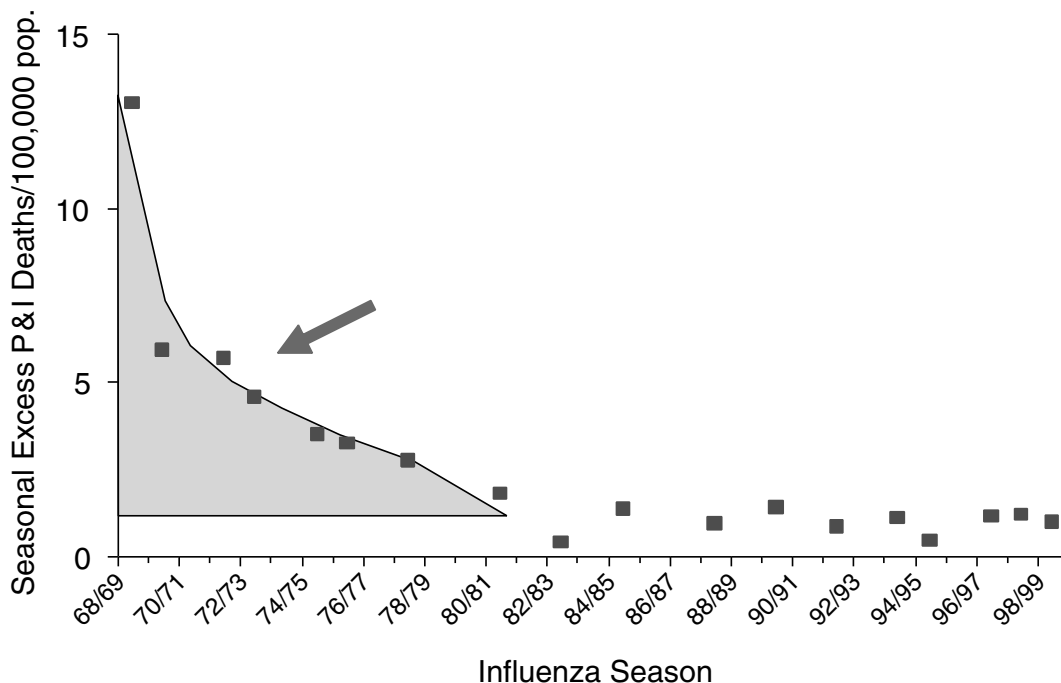


FIGURE 1-6 A pandemic “decade”: Seasonal excess pneumonia and influenza (P&I) mortality rates for A(H3N2)-dominated seasons remained elevated for a decade after 1968 in persons aged 45–64 years, United States, 1968–1999.

The age shift in mortality was even more pronounced in the 1918 A(H1N1) Spanish influenza pandemic (Collins, 1931; Simonsen, 1998; Olson et al., 2004).

### The 1968 Hong Kong Pandemic: Some New Observations

#### *The Unimpressive Impact of the 1968 Pandemic on Mortality in the United States*

The 1968 pandemic is the only one known in which a shift in the hemagglutinin antigen was not accompanied by a shift in the neuraminidase antigen. Perhaps for that reason, the 1968 pandemic mortality impact was not particularly severe compared to the severe epidemic in 1967–1968 (the last A(H2N2) epidemic), as well as two severe H3N2 epidemics in 1975–1976 and 1980–1981 (Table 1-2). People aged 75 years and older were far less likely to die of influenza during the pandemic than during these three surrounding epidemics, whereas people aged 45–64 years were at nearly three-fold elevated risk. Despite the differences in *relative* risk among age groups in different years, the *absolute* risk of dying of influenza during the pandemic was about 3 times higher for the elderly than for the younger age group (Table 1-2).

**TABLE 1-2** The Age-Specific Impact of the 1968 Pandemic in the United States\*: Comparison to Surrounding Severe Epidemics

	Excess All-Cause (and P&I) Deaths/100,000 Population		
	All Ages	75+ Years of Age	45–64 Years of Age
1967–1968 A/H2N2 epidemic	18 [6.3]	349 [107]	14 [3.6]
1968–1969 A/H3N2 pandemic	19 [9.1]	131 [79]	37 [13.0]
1975–1976 A/H3N2 epidemic	8 [6.5]	222 [113]	5 [3.2]
1980–1981 A/H3N2 epidemic	23 [4.3]	316 [70]	15 [1.8]

\*Winter-seasonal excess mortality rates (crude rates, unpublished data, Simonsen et al.) estimated by applying a Serfling (Serfling, 1963) model to U.S. monthly mortality data from 1967–1982.

*Virtues of Antigenic Sin: The Sparing of the Elderly*

Sero-archaeological studies have demonstrated that the majority of the very elderly had H3 antibodies before they were exposed to the 1968 A(H3N2) pandemic virus (Dowdle, 1999; Marine and Workman, 1969). These antibodies were remnants of the immune response to exposure to H3N2 viruses that circulated before 1891 (Marine and Workman, 1969); thus, the 1968 pandemic virus apparently contained an H3 antigen “recycled” after 77 years of absence. Marine and Workman hypothesized that the pre-existing anti-H3 antibodies were the result of “original antigenic sin” (Davenport et al., 1953)—childhood exposure to H3 antigens—and that these antibodies might have protected the elderly during the 1968 A(H3N2) pandemic (Marine and Workman, 1969). We recently confirmed this hypothesis when we used U.S. national mortality data to demonstrate that people over the age of 77 were, in fact, protected from influenza-related mortality during the 1968 pandemic, compared to surrounding severe non-pandemic seasons (Simonsen et al., 2003). Even so, the absolute risk of dying from 1968 pandemic influenza was always highest among the very elderly, although this risk was likely significantly lower than it would have been without the protection provided by the anti-H3 antibodies still present in this age group. Figure 1-7 shows the several-fold increase in

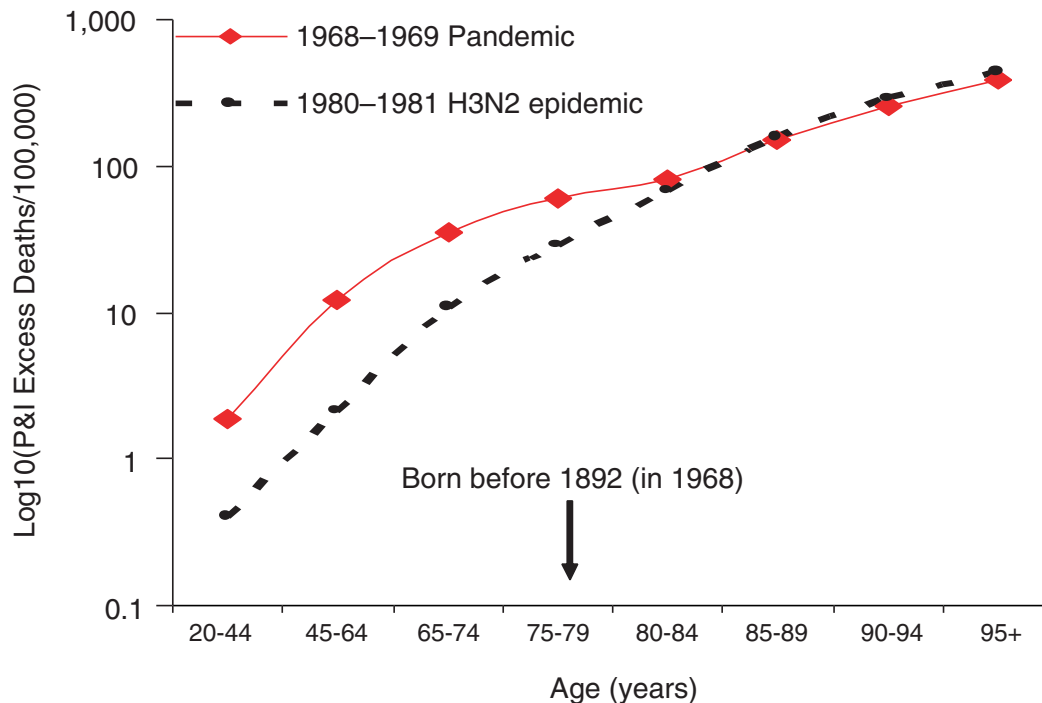


FIGURE 1-7 Evidence of protection of the very elderly by “virtues of antigenic sin”: Age-specific excess P&I mortality rates for the 1968 pandemic compared to the 1980–1981 season.

pneumonia and influenza (P&I) mortality rates during the 1968 pandemic among younger age groups in the United States compared to the 1980–1981 season, and the absence of any such increase among the very elderly.

These findings have significant implications for both pandemic planning and the prioritization of high-risk groups for vaccination in the scenario of vaccine shortage. Indeed, if one wishes to minimize the number of years-of-life-lost should vaccine be in short supply, then it would be more effective to immunize the middle aged and younger elderly than the very elderly.

### *The European 1968 Experience: A “Smoldering” Pattern*

The 1968 pandemic experience in Europe was different from that of the United States. It began with the rapid spread of a new virus, which reached Europe about 2 months after its emergence in Hong Kong (Cockburn et al., 1969). But influenza activity remained curiously weak in the wave that occurred during the 1968–1969 winter in Europe (Assaad et al., 1973; Stuart-Harris, 1970). At the same time, influenza-related mortality and morbidity increased substantially in the United States, especially among the young (Housworth and Spoon, 1971). More surprising, a much more severe wave occurred in the United Kingdom during the winter of 1969–1970, although no change in the circulating strain had been identified (Miller et al., 1971). We revisited the pandemic experience in the United States and the United Kingdom by extending the analysis of mortality data from both countries (Figure 1-8) to better describe and possibly explain the geographical differences.

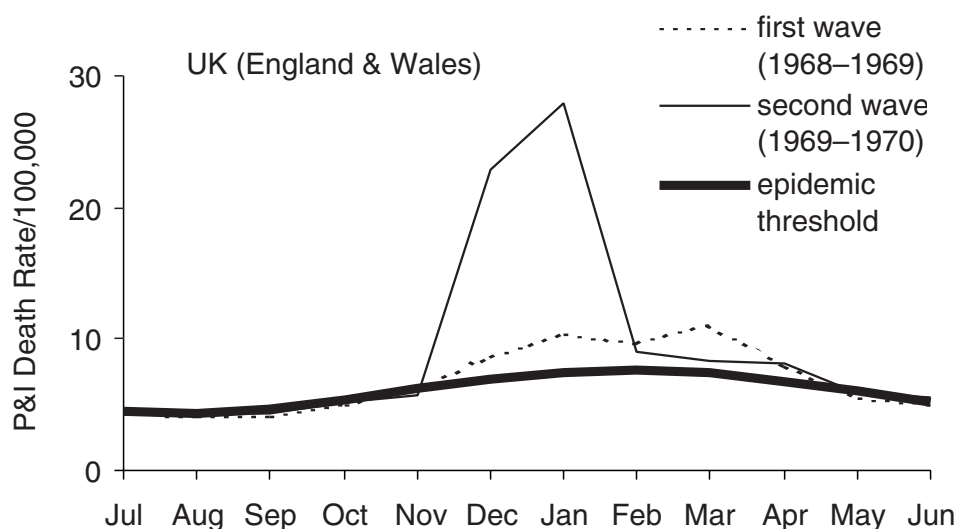


FIGURE 1-8 Monthly pneumonia and influenza (P&I) mortality rate during the first two waves of the 1968 pandemic (A/H3N2) in the United Kingdom. Epidemic threshold determined by a spline-Serfling regression model.

**TABLE 1-3 Comparison of the Relative Impact\* of the First Two Waves of A/H3N2 Viruses and the Age Distribution of Influenza Deaths in the United States and United Kingdom, 1968–1970**

A/H3N2 Pandemic seasons	USA (population: 205 million)		UK (England and Wales) (population: 48 million)	
	Relative impact of each wave [derived from excess P&I mortality rate/100,000 (all ages)]	Proportion of excess P&I deaths in persons under 65 years of age	Relative impact of each wave [derived from excess P&I mortality rate/100,000 (all ages)]	Proportion of excess P&I deaths in persons under 65 years of age
1968/1969 (1st wave)	70%	38%	22%	20%
1969/1970 (2nd wave)	30%	37%	78%	25%
Total pandemic impact (sum of 2 seasons)	100%	38%	100%	24%

\* All figures are standardized with regard to the 1969 population of England and Wales and based on a Serfling regression “spline” model applied to monthly data.  
 SOURCE: Viboud et al. (2004).

In both countries, we studied the age distribution of mortality rates associated with the first and second pandemic waves of A/H3N2, which occurred during the winters of 1968–1969 and 1969–1970 (Table 1-3). Consistent with the epidemiologic signature of a pandemic (Simonsen et al., 1998), a mortality shift towards younger age groups was observed simultaneously in both the United States and United Kingdom. The shift in the first pandemic wave (1968/1969) in the United Kingdom was not quite as definitive, but was nonetheless above the background of preceding epidemic seasons. In both countries, the proportion of deaths in younger age groups was highly elevated in the second wave. This age shift is consistent with the fact that virus surveillance systems reported widespread circulation of A(H3N2) in both countries during both seasons (Miller et al., 1971; Housworth and Spoon, 1971).

Because pneumonia mortality rates throughout the year were more than two-fold higher in the United Kingdom than in the United States during the 1950s and 1960s (Langmuir and Housworth, 1969; WHO, 1971), direct comparison of the *absolute* excess P&I mortality impact of the two pandemic waves is less revealing than their *relative* impact. In the United States, the first wave (1968–1969) accounted for 70 percent of the pandemic deaths, and the second season accounted for the remaining 30 percent. In the United Kingdom, however, the proportions were reversed: the first wave accounted for only 22 percent of UK pandemic deaths, whereas the remaining 78 percent occurred in the second (Table 1-3). Given that circulation of the pandemic virus is well-documented, we use the term “smoldering pandemic” to characterize the first wave in the United Kingdom—the pandemic started slowly, but built to a more destructive conflagration in the second season. We are currently studying other countries, and it thus far appears that the UK pattern describes the typical “European” 1968 pandemic experience (Stuart-Harris, 1970), while the U.S. pattern appears to represent the North American experience (Viboud et al., 2004).

The impact of a novel influenza virus is thought to decrease over time as immunity increases in the population (Cox and Subbarao, 2000; Miller et al., 1971). The European 1968 pandemic pattern, with its smoldering delay, did not fit this pattern, however. More than 30 years later, the reasons for the “smoldering waves” and the differences between North America and Europe are not clear (Nguyen-Van-Tam and Hampson, 2003). It is possible that in Europe only, a high level of immunity to neuraminidase N2 protected the population during the first A/H3N2 wave (Stuart-Harris, 1970). Such immunity would have been acquired through past exposure to A/H2N2 viruses. The “immunity” hypothesis is supported by a high rate of asymptomatic illnesses reported during the first pandemic wave in Europe (Miller et al., 1971; Sohier and Henry, 1969). Alternatively, the different patterns may be due to minor genetic differences in the A/H3N2 viruses that circulated on the two continents. This hypothesis is difficult to address

because only a very limited number of influenza A(H3N2) genetic sequences from the 1968–1970 period are available in the public domain. A new influenza genomics initiative recently funded by the National Institute of Allergy and Infectious Diseases (NIAID) should help change this situation, however. Under this program the Institute for Genomic Research (TIGR) will sequence qualified and properly prepared influenza virus samples for investigators (<http://www.niaid.nih.gov/dmid/genomes/mscs/projects.htm>). This initiative should encourage scientists everywhere to dig out old isolates sitting quietly in laboratory freezers, so that their complete sequences can be placed in GenBank for all to use.

From the perspective of pandemic planning, the smoldering European 1968 pandemic experience is encouraging, in that a repeat of this pattern in a future pandemic might allow the production and distribution of pandemic vaccines to occur in time to prevent a great many deaths. Indeed, had an effective pandemic vaccine become available in Europe even a full year after the emergence of A(H3N2) viruses in 1968, the majority of deaths associated with this pandemic might have been prevented. Whether smoldering patterns will occur in future pandemics is, of course, not known.

### **The 1957 Asian Pandemic: Impact Over Several Seasons**

The 1957 influenza pandemic, which claimed the lives of more than one million people worldwide, has long been an unofficial model scenario for a future pandemic in the United States. In order to increase the utility of this model for pandemic planners, we have recently begun to compare the well-characterized mortality patterns observed in the United States during the pandemic (Serfling et al., 1967) with those of other countries.

#### *The U.S. Experience: Three Waves Between 1957 and 1963*

The Asian H2N2 influenza virus is thought to have first emerged in China in February or March 1957. It reached the United States in early summer, at which time it caused sporadic outbreaks (Jordan, 1958a; Dunn, 1958). However, a measurable impact on U.S. mortality did not occur until October (Serfling et al., 1967). Moreover, each of the first three seasons dominated by the emerging A(H2N2) virus—1957–1958, 1959–1960 and 1962–1963—resulted in roughly equivalent spikes in excess P&I mortality rates in the U.S. population (Serfling et al., 1967) (Table 1-4). These observations suggest that the second twentieth century pandemic did not strike in a sudden, overwhelming onslaught. Instead, measurable mortality impact occurred 4 to 6 months after the virus had begun to circulate and was isolated.

Serfling's analyses of the U.S. data also revealed that of all the deaths that occurred among age groups 45 years or younger during the first three

serious H2N2 seasons, the majority occurred in the pandemic season of 1957–1958. Conversely, those 45 years and older felt the majority of the mortality impact in the next two A(H2N2)-dominated seasons, 1959–1960 and 1962–1963. For example, 71 percent of the excess deaths among 15–19 year olds in all three seasons occurred during the pandemic 1957–1958 season, while for people aged 75 and older only 33 percent of excess deaths occurred in the pandemic season (Table 1-4). These differences in age-related mortality patterns closely reflected differences in age-specific attack rates of the influenza virus, which were available from the Cleveland Family Study (Jordan et al., 1958a) and Tecumseh, Michigan (Hennessy et al., 1964). Indeed, the attack rate among school children was very high (72.9 percent) in 1957–1958 (Jordan et al., 1958b), but far lower in 1959–1960 and 1962–1963 (Hennessy et al., 1964). It was considered possible that the lower 1957–1958 attack rates left a larger proportion of susceptible people among older cohorts during the subsequent seasons (Hennessy et al., 1964). In summary, the bulk of A(H2N2) infection and mortality among younger age groups occurred in 1957/1958; much less occurred in the subsequent seasons, during which these younger age groups were probably protected by immunity gained through their first encounter with A(H2N2) viruses. However, for the middle aged and elderly, the “pandemic” impact was almost evenly divided between the first three seasons dominated by A(H2N2) viruses (Serfling et al., 1967).

To investigate whether this age-specific mortality pattern also describes the international experience, we set out to develop a methodology for

**TABLE 1-4** Relative Impact of First Three “Waves” of A(H2N2) Influenza in the United States, 1957–1963 (modified from data in Serfling et al., 1967)

Pandemic	Excess P&I Mortality Rate/100,000 Population in the United States and the [Proportional Contribution to the Total for Three Seasons]		
	All Ages	School Children 5–14 Years of Age	Elderly 75+ Years of Age
1957/1958	10.6 [44%]	1.5 [75%]	97 [33%]
1959/1960	7.4 [30%]	0.3 [15%]	102 [35%]
1962/1963	6.3 [26%]	0.2 [10%]	94 [32%]
Total pandemic impact (sum of 3 seasons)	24.3 [100%]	2.0 [100%]	293 [100%]

**TABLE 1-5** Relative impact of first 3 “waves” of A(H2N2) influenza in JAPAN, 1957–1963 (data from Heiman et al., unpublished)

Pandemic	Excess P&I Mortality Rate/100,000 Population in Japan and the [Proportional Contribution to the Total for Three Seasons]		
	All Ages	School Children 5–14 Years of Age	Elderly 75+ Years of Age
1957/1958	1.8 [44%]	1.9 [79%]	29 [36%]
1959/1960	0.9 [30%]	0.2 [8%]	18 [22%]
1962/1963	1.3 [26%]	0.3 [13%]	34 [42%]
Total pandemic impact (sum of 3 seasons)	4.0 [100%]	2.4 [100%]	81 [100%]

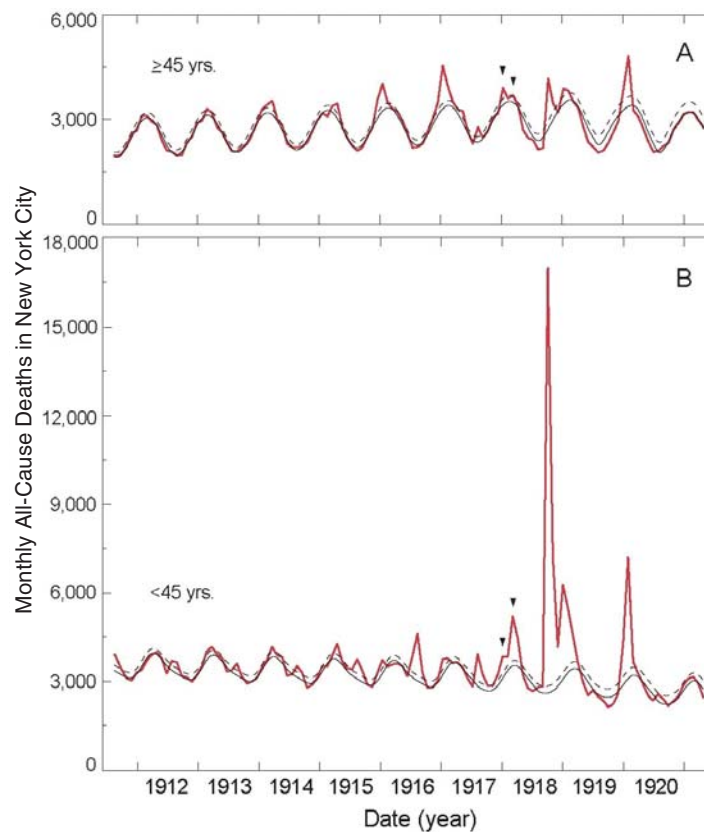
measuring pandemic mortality burden based on annual mortality data (Heiman et al., unpublished). Annual age-specific P&I mortality data were provided by WHO for the United States and Japan. We estimated the pandemic excess mortality in 1957 and 1958 by subtracting as background the number of deaths in surrounding years when there was little or no influenza A activity. We validated this approach by comparing these U.S. age-specific excess mortality estimates with those generated using actual seasonal data (Serfling et al., 1967). We found that for Japan, the age pattern of relative impact over the first seasons was very similar to that observed in the United States (Table 1-5). Also, in contrast to the United States where there was no measurable increase in influenza-related mortality until October, P&I mortality in Japan was elevated in the early summer of 1957 (Reichert et al., 2001).

### **The 1918 Spanish Influenza Pandemic Revisited: Evidence for a Severe Herald Wave and Protection of the Elderly in New York City**

The exact time and place that the 1918 pandemic virus originated has never been conclusively determined. Public health investigators recognized almost immediately that the so-called Spanish influenza, which spread across Europe in the late spring and summer of 1918 and exploded globally in the autumn and winter of 1918/1919, probably did not originate in Spain (Low, 1920). Reports of influenza epidemics in U.S. military training camps in spring 1918, however, led some to identify the central United States as the “presumptive primary focus” of the pandemic (Vaughn, 1921).

Although this hypothesis has been cited many times over the years, it has never been subject to rigorous reexamination. Moreover, an old analysis of regional urban U.S. mortality statistics showed that excess mortality increased in several Atlantic seaboard cities in the spring of 1918, especially in New York City, suggesting that perhaps the pandemic strain might already have been spreading in this region (Frost, 1919).

To investigate whether and when the characteristic age shift occurred in influenza seasons preceding the 1918–1919 pandemic season in the United States, age-stratified excess deaths in New York City were analyzed (Olson et al., 2004). Comparison of all-cause mortality data for people over and under age 45 indicated that a shift in age-specific excess mortality happened very early in 1918, in the midst of an ongoing influenza season. This pattern is consistent with the arrival of the pandemic virus in New York City at about this time, and the subsequent occurrence of a pandemic herald wave from February to April 1918 (Figure 1-9, Table 1-6).



**FIGURE 1-9** Monthly all-cause deaths in New York City by age. Classic Serfling model estimates of baseline mortality and 95 percent confidence limits were calculated for under-45 [B] and 45-and-over [A] all-cause deaths. The seasonal pattern indicates that the 1917–1918 influenza season (arrowheads) showed two periods with distinct age-specific peaks. (Figure modified from Olson et al., 2004.)

**TABLE 1-6 Age-Specific Mortality Impact of the 1918–1919 A(H1N1) Pandemic in New York City (Population: 5 million) and During the “Herald Wave” in Early 1918 (modified from Olson et al., 2004)**

Age Groups (years of age)	Pre-Herald Wave	Herald Wave	Major Pandemic
	January 1918 All-Cause Excess Mortality Rate/100,000 Population	February–April 1918 All-Cause Excess Mortality Rate/100,000 Population	September 1918–March 1919 All-Cause Excess Mortality Rate/100,000 Population
<5	84	230	720
5–14	2	21	190
15–24	5	64	580
25–44	7	38	760
45–64	18	14	210
65+	190	95	150
All ages	21	56	530

The New York City data also demonstrate that mortality among people aged 45 and older during the 1918–1919 pandemic influenza season was no worse than in surrounding years. For people under age 45, however, the 1918–1919 influenza season was very bad—people in this age group were far more likely to die of influenza than in previous years. Indeed, the age groups at highest *absolute* risk of dying during the 1918–1919 A(H1N1) pandemic were young children and young and middle-aged adults (Table 1-6).

These findings suggest that the early 1918 pandemic herald wave was spreading as early as February 1918, 6–7 months before the beginning of the explosive 1918–1919 pandemic. Relative to preceding influenza epidemic seasons, both the herald and pandemic waves caused proportionally more mortality in younger age groups but less mortality among those over 45 years of age, possibly as the result of recycling of an H1-like antigen from half a century earlier (Olson et al., 2004).

### **Conclusion: Lessons from Pandemics Past for Pandemics Still to Come**

Epidemiologic studies of past pandemics offer at least three important insights into what we can expect when the next influenza pandemic occurs. We believe these observations can help to guide pandemic detection and preparedness planning.

1. *Mortality impact is difficult to predict, but a shift to younger ages is highly likely.* Because our experience with pandemic influenza is so limited ( $N = 3$ ), it is difficult to predict the mortality impact of a future pandemic. One can say, however, that the likely range is wide (from ~20 to ~500 deaths per 100,000 people) and that people under 65 years of age will account for a high proportion of these deaths.

2. *Pandemic mortality impact is not always “tornado-like.”* Pandemic influenza is not always like a sudden storm, followed by a return to clear skies. Instead, mortality rates can remain elevated for several years—during which time an effective vaccine would be in high demand. For example, in the 1957 pandemic worldwide, and in the 1968 pandemic in North America, much of the pandemic mortality impact occurred in a series of smaller but still severe twisters in subsequent years. This seems well explained by attack rates: The pattern of cumulative age-specific mortality impact during the first waves mirrored the age-specific attack rates, at least for the 1957 pandemic (Serfling et al., 1967). Thus, the majority of middle-aged and elderly people—age groups that account for most of the cumulative pandemic mortality—were only affected by the emerging strain during the second or third season after its emergence.

3. *Often there is a warning.* For the 1918 pandemic, a herald wave that caused substantial mortality occurred at least 6 months before the

major force of the pandemic hit in September. The 1957 pandemic virus had been characterized in Asia by the spring and was known to be circulating in the United States as early as June—months before the pandemic mortality impact began. For the 1968 pandemic, the majority of European deaths occurred after a 1-year delay. Thus, in all three pandemics, some form of warning was available.

Although mortality data are useful to characterize the patterns and impact of past pandemics, in most countries such data would not be available to allow timely detection of mortality age shifts to reveal pandemic activity. Instead, influenza virus surveillance efforts are most likely to provide the first warning of a future pandemic. And because younger people are disproportionately infected by pandemic strains when these first emerge, focusing pandemic virus surveillance efforts on isolates from children and young adults with severe outcomes of upper respiratory diseases would help to ensure that pandemic activity is detected as quickly as possible.

The idea that the next pandemic may not do all or even most of its damage in the first season is certainly good news for preparedness planning. In all three pandemics in the twentieth century, the majority of associated deaths occurred 6 months to a year *after* the pandemic virus first emerged. This suggests that intense and timely surveillance of both age-specific mortality and new influenza viruses could provide sufficient time for production and distribution of vaccines and antivirals to prevent much, if not most, of the mortality impact. Moreover, these medical interventions are likely to continue to play an important role for many years after the pandemic season. One should also note that the 1957 and 1968 pandemics tended to respect normal seasonality patterns, giving one hemisphere of the world an extra 6 months to prepare.

Finally, the existence of the pandemic age shift documented for all pandemics studied raises a crucial question: Who should get vaccines and antivirals first if these are in short supply, younger people or the elderly? If a future pandemic were to be like the severe 1918/1919 pandemic, in which young and middle-aged adults were the age groups at highest absolute risk of dying, then younger people should clearly get priority. But if a future pandemic were like the 1957 or the 1968 pandemics, the answer would not be so obvious. In those years, young and middle-aged adults were facing the most dramatic risk increase relative to non-pandemic influenza, yet they remained at a lower absolute risk than the elderly. The situation would be made more complex if the pandemic virus were to contain a recycled influenza antigen. In this instance, elderly age groups with prior exposure to similar antigens might be at less risk than in preceding non-pandemic seasons.

Of course, with or without recycling, a pattern like those seen in 1957 or 1968 would result in the elderly having a higher absolute risk of death.

If the metric used to measure effectiveness of vaccination were “numbers of deaths prevented,” then perhaps the elderly should be given priority—assuming they can produce an adequate antibody response to the pandemic vaccine. But if the concern is to minimize the years-of-life-lost, then the vaccine may be better used in young and middle-aged adults. This point was illustrated in a paper that sought to determine vaccination priorities by age and risk status; when basing priority on “returns due to vaccination,” an endpoint that is heavily influenced by years of life lost, the young and middle aged rose to the top of the priority list (Meltzer et al., 1999). Other authors have proposed that children be given priority to receive pandemic vaccine (Stuart-Harris, 1970; Longini et al., 1978; Reichert et al., 2001) and antivirals (Longini et al., 2004) in order to reduce transmission in the community and thereby indirectly reduce influenza impact among the elderly. The 2004 U.S. Pandemic Influenza Preparedness and Response Plan developed by the National Vaccine Program Office has not yet defined such priority groups (DHHS, 2004:24).

Given the very different proposals for how to best employ pandemic vaccines and antivirals should a shortage occur, we urge that a framework for determining priority groups be developed immediately. Such a scheme should be agreed on beforehand and be flexible enough to adapt to the likely level of disaster at hand. Any such an assessment would depend on rapid interpretation of early data on transmissibility and case fatality in the pandemic epicenter.

Will the next pandemic be 1918-like or 1957/1968-like? That is the question.

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